A monoclonal antibody that depletes blood stem cells and enables chemotherapy free transplants

Grant Award Details

A monoclonal antibody that depletes blood stem cells and enables chemotherapy free transplants

Grant Type: Disease Team Therapy Development - Research

Grant Number: DR2A-05365

Project Objective: The Goal of the project is to assess the safety and preliminary efficacy of a humanized anti-CD117 mAb as a chemotherapy free conditioning for allogeneic HSC transplants in patients with severe combined immunodeficiency (SCID).

Investigator:

Name:	Judith Shizuru
Institution:	Stanford University
Type:	PI

Disease Focus: Immune Disease, Pediatrics, X-linked Severe Combined Immunodeficiency (X-linked SCID), Blood Disorders

Human Stem Cell Use: Adult Stem Cell

Award Value: $19,068,382

Status: Active

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Grant Application Details

Application Title: A monoclonal antibody that depletes blood stem cells and enables chemotherapy free transplants

Public Abstract:

Successful stem cell therapy requires the replacement of diseased or dysfunctional stem cells with healthy ones. These healthy stem cells can come from either a donor or can be stem cells that are modified by gene therapy techniques. One important step in this process of repair and replacement is to eliminate the existing diseased cells so that physical space is created for the healthy ones, and competition for environmental factors that nurture and support the stem cells are removed.

The oldest and most commonly used form of stem cell therapy is bone marrow transplantation (BMT). Thousands of patients undergo BMT yearly to treat cancers or disorders of blood formation. Bone marrow contains mixtures of cells, but only a minority are the blood forming stem cells, which are critically important as only stem cells can permanently generate new blood and immune cells. In a BMT, stem cells from a donor replace the recipient's diseased stem cells. Currently, the only way to eliminate the patient's own blood forming stem cells is to treat the recipient to accept donor cells with toxic agents such as radiation and chemotherapy.

Our team will focus on the treatment of a disorder in children called severe combined immune deficiency (SCID). SCID children are born without a functional immune system and are therefore extraordinarily susceptible to serious infections. If children with SCID are not treated, most die by the age of two. BMT is the only established cure for this disease. Unfortunately, the likelihood of successful cure is reduced by the way transplants are currently performed, using toxic treatments to prepare the children to accept the donor cells.

We will test an antibody (a type of protein) that recognizes a molecule called CD117 present on blood forming stem cells and leads to their elimination. When used in mice, this treatment enabled excellent donor stem cell engraftment and cured mice with a condition equivalent to human SCID with minimal side effects. We propose to test an antibody that targets human CD117 to safely prepare children with SCID to accept blood forming stem cells from a donor. Based on the animal studies we expect this antibody will allow engraftment of stem cells at high levels, rapidly replacing diseased blood cells with healthy blood cells. Such a result would mean safer and better outcomes for these patients.

Success in this study would have impact far beyond a superior treatment for SCID. If the antibody treatment results in a stronger blood system originating from a donor in SCID patients, this result would prove that the antibody could be used to optimize engraftment of gene-therapy modified cells and could be applied to the treatment of many other diseases that need a BMT. These diseases include, but are not limited to sickle cell anemia, thalassemia, and Fanconi's anemia; autoimmune diseases like diabetes and multiple sclerosis; and cancers that originate from the blood system such as leukemias and lymphomas.

Statement of Benefit to California:

Diseases of the blood and the immune system plague thousands of Californians and millions of people world-wide. These diseases are quite diverse, ranging from blood diseases such as sickle cell anemia and beta thalassemia, to immune diseases such as severe combined immunodeficiency, HIV, and autoimmune disease including type I diabetes and multiple sclerosis. Current therapies do not fully control the symptoms of these diseases, leaving severe morbidity and early mortality as ongoing consequences. For the health of the citizens of California, both physical and financial, we need to develop cures, rather than marginally effective treatments, for a variety of these devastating blood and immune illnesses.

Hematopoietic stem cell (HSC) transplantation possesses the ability to provide a life-long cure for all of these diverse diseases, as it allows for the replacement of defective HSC. Although effective, the use of this form of treatment is severely limited because of the current need to administer chemotherapy or radiation prior to the transplant to permit engraftment of donor stem cells. The transplant procedure itself carries a risk of death for ~10-20% of patients, and there are long-term toxicities associated with chemoradiation such as infertility, secondary malignancies, endocrine dysfunction, organ damage, and in children, mental and physical growth impairment.

By developing a novel, non-toxic antibody-based conditioning method, HSC transplants could be expanded to the treatment of non-life threatening yet debilitating diseases that are currently not transplanted due to the associated toxicities. We have achieved this goal with an antibody in mice and have identified a similar agent for use in patients. We aim to begin safely treating patients that suffer from severe combined immunodeficiency (SCID), a diverse disorder that is caused by defects in HSCs. While the incidence of SCID has been thought to be rare, preliminary results of newborn screening in California suggest the incidence is 1/30,000 newborns. In addition, a number of previously treated patients with SCID who did not engraft with donor stem cells are now developing immune failure. The clinical trial to be performed will treat immunodeficient patients from across the state of California through the network of institutions incorporated into this disease team of world-renowned stem cell and transplantation experts.

After successfully treating patients with SCID, we plan to expand this conditioning technique to other diseases, and hopefully pave the way for safe transplantation of genetically modified HSC, thereby expanding stem cell transplantation in California tremendously. We hope this novel conditioning regimen will result in a direct benefit to patients who suffer from blood and immune diseases, as well as create definitive treatments that will lead to a reduction of the massive health care burden these diseases inflict on patients and their families in California.
